Transanular Interactions in Difunctional Medium Rings, 6[1]

Spectroscopic Investigations of Bicyclic Amino Ketones

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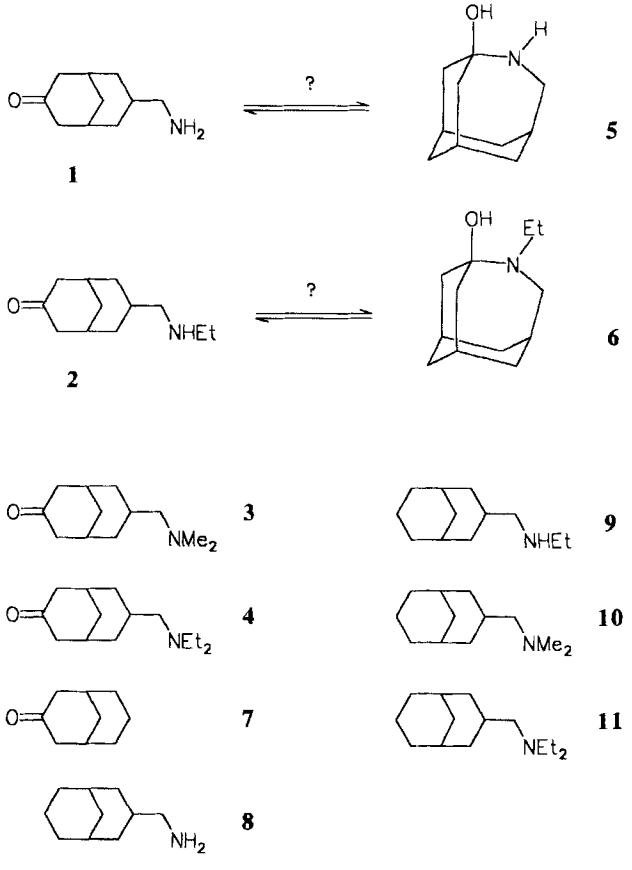
The *endo*-7-(aminomethyl)bicyclo[3.3.1]nonan-3-ones **1**–**4** with a primary, secondary, or tertiary amino group have been synthesized, and their tendency to form the corresponding tricyclic amino carbinols has been investigated by theoretical (MMX, AM1) and experimental (PE, ^{13}C-NMR spectroscopy) methods. Comparison of the characteristic spectroscopic properties of **1**–**4** with those of the isochromophoric monofunctional compounds **7**–**11** indicates that **1** and **2** form mixtures with the tricyclic isomers **5** and **6**, respectively, whereas **3** and **4** show no interactions between the amino and the carbonyl group in the solely present bicyclic structures.

Kovacic et al.[2,3] have investigated the intramolecular interaction in *endo*-7-(aminomethyl)bicyclo-[3.3.1]nonan-3-ones leading to tricyclic amino carbinols. While, mainly from IR and ^{1}H-NMR spectroscopic measurements, for the parent compound **1** the tricyclic isomer **5** has been found to prevail, for the *N*-ethyl derivative only the bicyclic amino ketone has been detected. We have now studied **1** and the *N*-alkyl and *N*,*N*-dialkyl derivatives **2**–**4** by different methods. As in preceding investigations[1] we have used molecular mechanics[4] and semiempirical quantum-chemical calculations (AM1[5]) as well as photoelectron (PE) spectroscopy[6] and NMR spectroscopy. The ketone **7** and the amines **8**–**11** have been included in this study as monofunctional reference compounds.

$n_N/\pi_{C=O}$ interaction (transanular amide resonance) in cyclic amino ketones of medium ring size has been studied by PE spectroscopy and other methods[7].



Syntheses

endo-7-(Aminomethyl)bicyclo[3.3.1]nonan-3-one[2] (**1**) or 6-hydroxy-5-azatricyclo[4.3.1.1^{3,8}]undecane(2-azahomoadamantane, **5**) and *endo*-7-[(ethylamino)methyl]bicyclo-[3.3.1]nonan-3-one[3] (**2**) or 5-ethyl-6-hydroxy-5-azatricyclo-[4.3.1.1^{3,8}]undecane (**6**) have been prepared by the methods described by Kovacic et al. Attempts to synthesize *endo*-7-[(methylamino)methyl]bicyclo[3.3.1]nonan-3-one have failed.

The synthesis of *endo*-7-[(dimethylamino)methyl]bicyclo[3.3.1]nonan-3-one (**3**) has proven to be more difficult than expected. Reaction of *endo*-7-(iodomethyl)bicyclo[3.3.1]nonan-3-one[8] (**12**) with aqueous dimethylamine in the presence of ethyldiisopropylamine at ambient temperature does not afford **3**, but by transanular cyclization tricyclo[4.3.1.0^{3,8}]decan-4-one[9] (**13**) is formed. The same product is obtained when **1** is treated with bromomethane[10] at reflux temperature in ethanol in the presence of potassium carbonate. If, however, the methylation is performed at ambient temperature in the presence of ethyldiisopropylamine, **3** is obtained in a yield of 64%. Alternatively, **1** is reduced to the alcohol **14**[11] which affords *endo*-7-[(dimethylamino)methyl]bicyclo[3.3.1]nonan-3-ol (**15**) by

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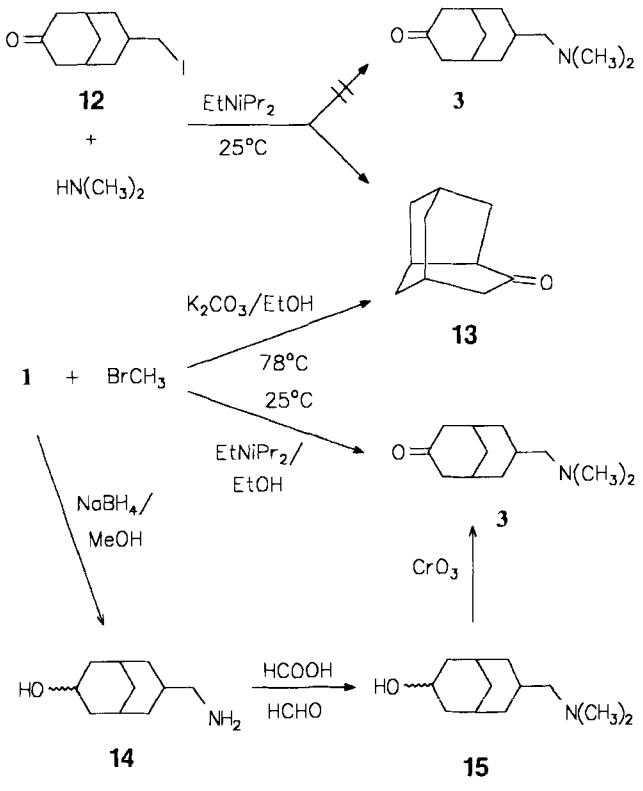
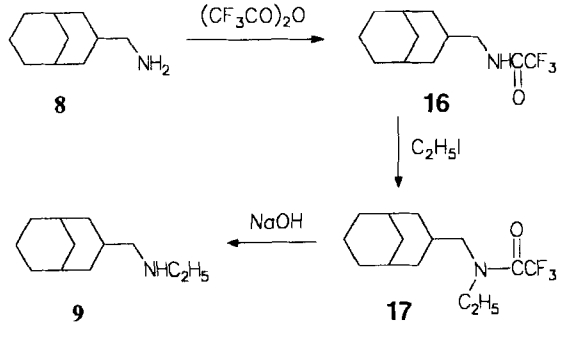
a Leuckart-Wallach methylation. Compound **15** is oxidized to **3** with chromium(VI) oxide.



endo-7-[(diethylamino)methyl]bicyclo[3.3.1]nonan-3-one (**4**) is obtained by reaction of the primary amine **1** with bromoethane. The secondary amine *endo*-3-[(ethylamino)-methyl]bicyclo[3.3.1]nonane (**9**) is synthesized from *endo*-3-(aminomethyl)bicyclo[3.3.1]nonane[12] (**8**) via **16** and **17**.



The ketone **7** is prepared as described by Hall[13]. The monofunctional amines *endo*-3-[(dimethylamino)methyl]-bicyclo[3.3.1]nonane (**10**) and *endo*-3-[(diethylamino)methyl]bicyclo[3.3.1]nonane (**11**) have been described[1].

Results

Structures

For the conformations of **1**–**4** and **8**–**11** the puckering of the bicyclic system and the orientation of the *endo* substituent are important. The conformation of the latter is measured by the torsional angle $C^2-C^3-CH_2-N$ for the amines and $C^6-C^7-CH_2-N$ for the amino ketones. We have studied the structures and the conformational properties of **1**–**11** by molecular mechanics[3] (MMX) and quantum-chemical (AM1[4]) calculations[14], but only some important and general results are mentioned here. The bicyclic system has either the chair-chair (CC) or the chair-boat (CB) form, and the substituent adopts an sc or ac conformation. As an example, the conformers of the amino ketone **1** are depicted in Figure 1. The acCB conformer has the lowest and the scCC conformer which is stabilized to a certain extent by an intramolecular hydrogen bond has the highest strain energy. Accordingly, the latter form which offers the optimal orientation of the two functional groups for intramolecular interactions at a rather short distance, should only contribute little to the conformational equilibrium.

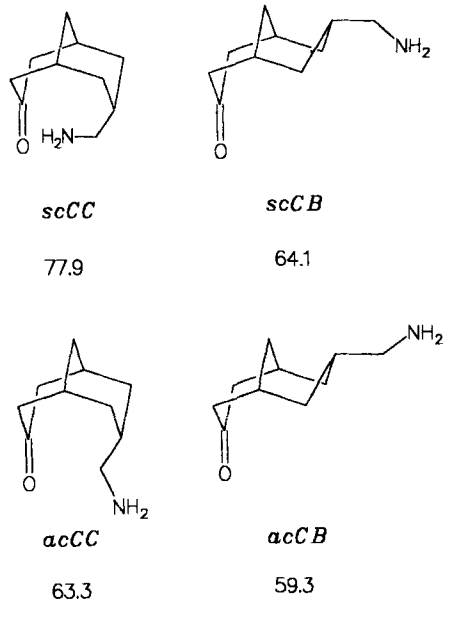


Figure 1. Conformers of amino ketone **1** with MMX strain energies [kJ mol^{-1}]

As far as the amino ketone-amino carbinol equilibrium is concerned, the AM1 method assigns nearly equal enthalpies of formation to **1** and **5**, whereas for **2**/**6** the bicyclic structure is clearly preferred to the tricyclic structure[14].

Electronic Structures

For the amino ketones **1**–**4** a n_N and a n_O orbital are expected as the two highest occupied molecular orbitals. Their energies are dependent on the mutual interactions of the two functional groups[7]. This effects also the $\pi_{C=O}$ orbital, but since this orbital has a rather low energy, and the corresponding ionization occurs in the range of broad σ bands, assignment is difficult and, therefore, this MO is not considered here.

The n_N and n_O eigenvalues calculated by the AM1 method for the amino ketones **1**–**4**, the amino carbinols **5** and **6**, bicyclo[3.3.1]nonan-3-one (**7**), and the amines **8**–**11** are

summarized in Table 1. The n_O orbital of the amino ketones remains nearly unshifted relative to its position in the ketone **7**. Also the energies of the n_N orbitals of **1**–**4** are found very close to their respective values in the amines **8**–**11**. It can hence be stated definitely that there are only negligible intramolecular interactions of the functional groups in the prevailing CB conformers of **1**–**4**. For the scCC conformers which have N···C distances between the functional groups of ca. 290–300 pm, a sizable stabilization is found for the n_O orbital up to 0.34 eV[14].

Table 1. Ionization potentials *IP* [eV] and orbital energies $-\varepsilon^{SCF}$ [eV] of the difunctional bicyclic compounds **1**–**4**, the monofunctional bicyclic compounds **7**–**11**, and the tricyclic compounds **5** and **6**

	IP		-ε[a]	
	n_N	n_O	n_N	n_O
1	(9.1)	9.05	9.77	10.24
5	8.49	9.78	9.40	10.59
2	8.61	9.02	9.35	10.18
6	7.86	9.62	8.92	10.53
3	8.21	8.95	9.15	10.15
4	7.96	8.95	9.00	10.14
7		9.05		10.21
8	9.12		9.73	
9	8.48		9.22	
10	8.18		9.06	
11	7.96		8.84	

[a] AM1 results. acCB conformation of **1**–**4**, **8**, **9**, CC conformation of **7**.

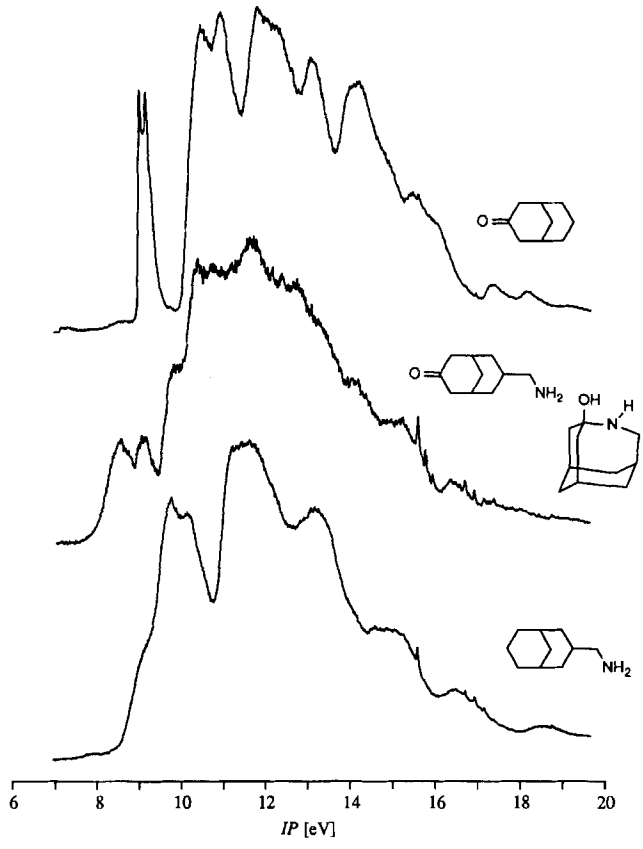


Figure 2. PE spectra of **1/5** and the corresponding monofunctional compounds **7** and **8**

For the amino carbinols **5** and **6** a n_N orbital is found as the HOMO and an orbital with a dominant n_O contribution is found as the second highest occupied MO. The formation of the tricyclic system from the bicyclic amino ketones causes a destabilization of the n_N of about 0.3 eV and a stabilization of the n_O of about 0.5 eV.

Photoelectron Spectra

Typical examples of the relevant PE spectra are shown in Figure 2. The observed ionization potentials of **1**–**11** are collected in Table 2. Comparison of the spectra of the difunctional with those of the monofunctional compounds allows assignments of the ionization potentials, which are supported by the results of the quantum-chemical calculations making use of the Koopmans approximation[15], $IP_v(i) \approx -\varepsilon^{SCF}(i)$.

For **1/5** the first ionization band has to be attributed to the n_N of the amino carbinol **5** since it is found at a clearly lower energy than in amine **8**. On the other hand, the second band is found at the same position as the n_O ionization of the carbonyl group of ketone **7** and very close to the n_N ionization of **8**, so it should be assigned to the corresponding ionizations of amino ketone **1**. Since, compared to **7** and **8**, the intensities of these bands are much lower, it is likely that in the gas phase there is an equilibrium of **1** and **5** with comparable amounts of both isomers. The third ionization of **1/5** should then originate from the alcoholic n_O of **5**. Changes in the intensities of the ionization bands are observed when the spectrum is recorded at different temperatures, which also is in accord with an equilibrium between **1** and **5**.

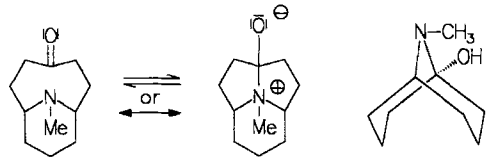
Similar results are found for **2/6**. The second ionization potential is very close to the n_N of **9**, and the third IP has nearly the same value as the n_O of **7**. These ionizations are assigned to amino ketone **2**. On the other hand, the first and the fourth IPs are assigned to n_N and n_O of **6**. In the mixtures **1/5** and **2/6**, the respective bicyclic isomers show no substantial interactions of the functional groups because their ionizations are found very close to the values of the monofunctional molecules.

For the tertiary amino ketones **3** and **4** the formation of an amino carbinol is not possible. The PE spectra of **3** and **4** show two bands in the low-energy region (< 10eV) which are due to ionizations from the n_N and n_O orbitals. Since deviations from the respective values of the monofunctional compounds **7** (n_O), **10** and **11** (n_N) are rather small (< 0.1 eV) no sizable transanular interactions can be ascertained.

^{13}C-NMR Spectra

Nakashima and Maciel[16] have shown for 11-methyl-11-azabicyclo[5.3.1]undecan-4-one (**18**) that transanular interactions in heterocyclooctan-5-ones can be detected by ^{13}C-NMR spectroscopy. In this case, the carbonyl carbon atom suffers a high-field shift of 12 ppm relative to that of cyclo-

octanone. The authors have observed an additional high-field shift of 70 ppm when instead of the solvent cyclohexane a mixture (10:90) of cyclohexane and chloroform is used. This can be explained by taking into account the occurrence of a zwitterionic structure **19**. Accordingly, a high-field shift of the signal of the carbonyl carbon atom of the amino ketones **1**–**4** relative to that of ketone **7** should indicate intramolecular interaction.



18 **19** **20**

The relevant ^{13}C-NMR data of the compounds studied here are collected in Table 2. The very low solubility of **1/5** permits measurement only in highly diluted solution. The resonance with the highest chemical shift is found as a weak signal at $\delta = 84-85$ and is assigned to the amino carbinol carbon atom. The analogous carbon atom of 9-methyl-9-azabicyclo[3.3.1]nonan-1-ol (**20**) is found at $\delta = 82.5$[17]. Since no signal is detected for a carbonyl carbon atom, the presence of amino ketone **1** can be excluded. Also the number of signals does not permit the presence of a second species. In addition, the tricyclic structure is supported by the δ^{13}C value of C-9 which is in the characteristic range of the CC conformation of a bicyclo[3.3.1]nonane skeleton which is also present in the tricycle **5**.

Table 2. δ^{13}C values of the carbonyl and the C-9 carbon atoms of the amino ketones **2**–**4**, the ketone **7**, and of the amino carbinol carbon atom of the amino carbinol **5** (in $CDCl_3$)

	>C=O	>N-CR_2-OH	C-9
2	212.8		32.8
3	212.2		29.0
4	212.2		29.1
5		84.9	34.7
7	213.1		

The situation seems to be different for the amino ketone **2**. Although the formation of the amino carbinol **6** in solution should be possible, no signal is found for the corresponding carbon atom. A weak signal is detected for the carbonyl carbon atom of **2**. Moreover, the chemical shift of C-9 is typical of the CB conformation of the bicyclic system **2**. The picture is completed by the IR spectrum. In CCl_4 solution there is no OH absorption at 3500 cm^{-1}, but a strong carbonyl band is found at 1700 cm^{-1}.

Since **3** and **4** cannot form an amino carbinol, high-field shifts of the signal of the carbonyl carbon atom might only be caused by intramolecular interactions. However, the minute shift of this signal relative to that of the ketone **7** for both compounds is at variance with such effects. The chemical shifts of C-9 indicate CB conformations of **3** and **4**.

Discussion

The intramolecular $n_N/\pi_{C=O}$ interaction in the amino ketones **1**–**4** has been studied by PE and ^{13}C-NMR spectroscopy supported by molecular mechanics (MMX) and semiempirical quantum-chemical (AM1) calculations.

Comparison of the PE spectra of **1/5** with those of the monofunctional compounds **7** and **8** indicates an amino ketone-amino carbinol equilibrium. The amino ketone **1**, present in the mixture, has a CB conformation which prevents intramolecular interaction of the functional groups. This is supported by the MMX and AM1 results[14], which indicate that the CC conformation which would enable effective $n_N/\pi_{C=O}$ interaction is not favorable for **1**. Our ^{13}C-NMR spectroscopic measurements show only the signals of the amino carbinol **5**. In the IR spectrum of a $CHCl_3$ solution of **1** a carbonyl band of medium intensity is detected at 1700 cm^{-1}[3] whereas in dioxane no such absorption is present, and a KBr pellet shows it at 1667 cm^{-1}. In the IR spectra it is not possible to assign the region 3300–3800 cm^{-1} unambiguously. Even an X-ray structure analysis does not give a final answer since disorder has been found for the relevant part of the molecule[14]. However, the CC conformation of the bicyclo[3.3.1]nonane skeleton and some of the structure parameters are in favor of a mixture of amino ketone **1** and amino carbinol **5** also in the crystalline state.

In the gas phase, also the secondary amino ketone **2** is accompanied by its isomeric amino carbinol **6**. However, in $CDCl_3$ solution only **2** is found. Compound **2** has a CB conformation which does not allow $n_N/\pi_{C=O}$ interaction. The deviations of **2/6** from **1/5** in solution may be the result of different solvation since **2** is – in contrast to **1/5** – well soluble in $CDCl_3$.

For the tertiary amino ketones **3** and **4** no intramolecular interactions can be ascertained in the gas phase as well as in solution. The bicyclic systems prefer a CB conformation, and $n_N/\pi_{C=O}$ interaction in the CC conformation is not strong enough to fix the molecule in this conformation.

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Experimental

For experimental details see ref.[18].

endo-7-[(Dimethylamino)methyl]bicyclo[3.3.1]nonan-3-one (**3**): Bromomethane is passed into 300 ml of ethanol until 50.0 g has dissolved. 262.67 g of this solution (0.28 mol of CH_3Br) is added dropwise under argon and with stirring within 2 h to a solution of 20.00 g (0.12 mol) of 7-(aminomethyl)bicyclo[3.3.1]nonan-3-one (**1**) and 35.0 g of ethyldiisopropylamine in 300 ml of ethanol. Stirring is continued at ambient temp. for 12 h. The ethanol is removed in vacuo at 30°C, and the solid residue is triturated with 100 ml of dichloromethane. To the resulting suspension 20 ml of a 10% sodium hydroxide solution is added. After stirring for 30 min the aqueous layer is extracted three times with 50 ml of dichloromethane. The combined extracts are dried with sodium sulfate, the solvent is removed by suction and the residue is distilled in vacuo. The product solidifies at room temp. Further purification is

achieved by Hinsberg separation. Yield of **3** 15.00 g (64%), b.p. 85°C/0.05 Torr, m.p. 40.5–41.5°C. – ^{1}H NMR ($CDCl_3$): δ = 2.47–0.82 (m, 13H), 2.15 [s, 6H, $N(CH_3)_2$], 1.96 (d, *J* = 7.3 Hz, 2H, CH–CH_2–N). – ^{13}C NMR ($CDCl_3$): δ = 26.9 (C-7), 28.3 (C-1, -5), 29.0 (C-9), 32.6 (C-6, -8), 45.7 [$N(CH_3)_2$], 49.8 (C-2, -4), 66.2 (CH–CH_2–N), 212.2 (C-3). – IR (KBr): $\tilde{\nu}$ = 2980–2810 cm^{-1} (CH_3, CH_2, CH), 2780 (N–CH_2), 1710 (C=O), 1460–1430 (CH_3, CH_2), 1030 (C–N). – MS, *m/z* (%): 195 (2) [M^+], 58 (100) [$H_2C{=}N(CH_3)_2^+$]. – $C_{12}H_{21}NO$ (195.3): calcd. C 73.85, H 10.77, N 7.18; found C 74.03, H 10.60, N 7.58.

endo-7-[(Diethylamino)methyl]bicyclo[3.3.1]nonan-3-one (**4**): To a solution of 16.45 g (98.0 mmol) of **1** in 350 ml of anhydrous ethanol is added dropwise with stirring within 1 h at ambient temp. 40.00 g (0.37 mol) of bromoethane. Stirring is continued for 1 h. Then 22.0 g of potassium carbonate is added, and the mixture is refluxed for 4 d. After removal of the insoluble components by filtration, the filtrate is evaporated to dryness. Further purification is achieved by Hinsberg separation. The obtained raw product is distilled in vacuo through a 10-cm Vigreux column. The product is a colorless viscous liquid. Yield of **4** 6.38 g (29%), b.p. 82°C/0.01 Torr. – ^{1}H NMR ($CDCl_3$): δ = 2.48 (q, *J* = 7.1 Hz, 4H, NC$H_2$$CH_3$), 2.39–0.85 (m, 15H), 2.05 (d, *J* = 7.1 Hz, 2H, CHCH_2N), 0.95 (t, *J* = 7.1 Hz, 6H, CH_3). – ^{13}C NMR ($CDCl_3$): δ = 11.7 (CH_3), 28.4 (C-7), 28.4 (C-1, -5), 29.1 (C-9), 33.0 (C-6, -8), 47.3 (N–$CH_2$$CH_3$), 49.9 (C-2, -4), 59.8 (CH–CH_2N), 212.2 (C-3). – IR (liquid): $\tilde{\nu}$ = 2980–2800 cm^{-1} (CH_3, CH_2, CH), 1710 (C=O), 1460–1420 (CH_3, CH_2), 1040 (C–N). – MS, *m/z* (%): 223 (2) [M^+], 86 (100) [$H_2C{=}N(C_2H_5)_2^+$]. – $C_{14}H_{25}NO$ (223.4): calcd. C 75.34, H 11.21, N 6.28; found C 75.41, H 11.55, N 6.33.

endo-3-[(Ethylamino)methyl]bicyclo[3.3.1]nonane (**9**)

endo-3-[(Trifluoroacetylamino)methyl]bicyclo[3.3.1]nonane (**16**): To a solution of 8.40 g (54.8 mmol) of 3-(aminomethyl)bicyclo[3.3.1]nonane (**8**) in 100 ml of anhydrous diethyl ether is added dropwise within 15 min under argon 14.20 g (67.6 mmol) of trifluoroacetic anhydride. The mixture is refluxed for 3.5 h. The solvent is removed by suction, and 100 ml of water is added to the residue. The solution is made alkaline by addition of a saturated aqueous potassium carbonate solution and extracted three times with 50 ml of diethyl ether. The combined extracts are dried with sodium sulfate. The solvent is removed by suction and the residue is distilled. The product solidifies in the receiver. Yield of **16** 9.05 g (66%), b.p. 103°C/0.3 Torr, m.p. 67°C. – ^{1}H NMR ($CDCl_3$): δ = 6.64 (broad, 1H, NH), 3.22 (t, *J* = 6.2 Hz, 2H, CHCH_2NH), 2.09–0.82 (m, 16H). – IR (KBr): $\tilde{\nu}$ = 3310 cm^{-1}, 3080 (N–H), 2970–2805 (CH_3, CH_2, CH), 1720 (C=O), 1475–1435 (CH_3, CH_2), 1570–1540 (N–C and N–H), 1220 (C–F). – MS (high resolution): 249.1436 (calcd. for $C_{12}H_{18}F_3NO$ 249.2407). – $C_{12}H_{18}F_3NO$ (249.2): calcd. C 57.83, H 7.23, N 5.62; found C 58.76, H 7.95, N 5.52.

endo-3-{[Ethyl(trifluoroacetyl)amino]methyl}bicyclo[3.3.1]nonane (**17**): To a refluxing suspension of 8.90 g (35.7 mmol) of **16** and 19.40 (0.14 mol) of potassium carbonate in 100 ml of acetone is added dropwise under argon within 2 h 21.20 g (0.14 mol) of iodoethane. The mixture is refluxed for 5 d. The insoluble components are removed by filtration, and the readily volatile ingredients are distilled off by suction. The remaining colorless oil is distilled through a 5-cm Vigreux column in vacuo. The product solidifies upon cooling. Yield of **17** 3.10 g (31%), b.p. 78°C/0.01 Torr, m.p. 31–32°C. – ^{1}H NMR ($CDCl_3$): δ = 3.49 (q, *J* = 2.3 Hz, 2H, NC$H_2$$CH_3$), 3.26 (d, *J* = 7.0 Hz, 2H, CHCH_2N), 2.08–0.73 (m, 15H), 1.22 (t, *J* = 8.1 Hz, 3H, CH_3). – IR (melt): $\tilde{\nu}$ = 2980–2820 cm^{-1} (CH_3, CH_2, CH), 1695 (C=O), 1470–1440 (CH_3, CH_2), 1120 (C–F), 1035 (C–N). – MS (high resolution): 277.1853 (calcd. for $C_{14}H_{22}F_3NO$ 277.3327). – $C_{14}H_{22}F_3NO$ (277.3): calcd. C 60.65, H 7.94, N 5.05; found C 61.50, H 8.62, N 4.94.

Bicyclononane **9**: A mixture of 2.5 g (9.0 mmol) of **17**, 3.0 g of potassium hydroxide, 50 ml of water, and 20 ml of ethanol is refluxed for 4 d. The solvents are removed by suction, and the residue is treated with 60 ml of water. The suspension is extracted twice with 25 ml of dichloromethane. The combined extracts are dried with sodium sulfate, the solvent is removed by suction, and the residue is distilled in vacuo. Yield of **9** 0.27 g (17%), b.p. 52°C/0.01 Torr. – ^{1}H NMR ($CDCl_3$): δ = 2.69 (q, *J* = 7.2 Hz, 2H, NC$H_2$$CH_3$), 2.48 (d, *J* = 6.5 Hz, 2H, C*H*–CH_2N), 2.02–0.68 (m, 16H), 1.16 (t, *J* = 7.2 Hz, 3H, CH_3). – ^{13}C NMR ($CDCl_3$): δ = 14.4 (CH_3), 15.8 (C-3), 25.4 (C-1, -5), 29.1 (C-9), 31.3 (C-6, -8), 33.4 (C-2, -4), 44.1 (CH_2CH_3), 56.2 (CH–CH_2N). – IR (Film): $\tilde{\nu}$ = 3360 (N–H), 2980–2840 (CH_3, CH_2), 1460–1440 (CH_3, CH_2), 1030 cm^{-1} (C–N). – MS, *m/z* (%): 181 (2) [M^+], 58 (100) [$H_2C{=}NHC_2H_5^+$]. – $C_{12}H_{23}N$ (181.2): calcd. C 79.56, H 12.71, N 7.73; found C 79.43, H 12.14, N 8.19.

endo-7-[(Methylamino)methyl]bicyclo[3.3.1]nonan-3-one

N-Adamantyl-2,2,2-trifluoroacetamide: 22.00 g (0.15 mol) of 1-aminoadamantane is dissolved under argon in 300 ml of anhydrous diethyl ether. Within 1.5 h 32.40 g (0.15 mol) of trifluoroacetic anhydride is added dropwise to the solution. The mixture is refluxed for 4 h. The solvent is removed at reduced pressure, and to the remaining viscous liquid is added 100 ml of water. A white solid is formed at once which is filtered off by suction, washed with a large amount of water, dried in the air, and then dissolved in anhydrous acetone. After drying with magnesium sulfate the acetone is removed by suction, and the residue is dried in vacuo. Yield 30.1 g (84%), m.p. 92–94°C. – ^{1}H NMR ($CDCl_3$): δ = 6.0 (broad, 1H, NH), 2.05 (broad, 3H, >CH–), 2.04 (d, *J* = 2.9 Hz, 6H, CH_2N), 1.71 (t, *J* = 2.9 Hz, 6H, CH_2). – IR (KBr): $\tilde{\nu}$ = 3310 cm^{-1}, 3080 (N–H), 2970–2820 (CH_2, CH), 1550 (N–C and NH), 1450 (CH_2), 1220 (C–F). – MS, *m/z* (%): 246 (66) [M^+ – 1], 92 (100). – $C_{12}N_{16}F_3NO$ (247.3): calcd. C 58.29, H 6.48, N 5.76; found C 58.42, H 6.48, N 5.41.

N-Adamantantyl-2,2,2-trifluoro-N-methylacetamide: A mixture 28.40 g (0.12 mol) of *N*-adamantyl-2,2,2-trifluoroacetamide, 65.00 g (0.46 mol) of iodomethane, 26.0 g (0.45 mol) of pulverized potassium hydroxide, and 200 ml of anhydrous acetone is refluxed for 12 h. Excess iodomethane and acetone are removed by suction, and 100 ml of water is added to the residue. The suspension is extracted three times with 50 ml of diethyl ether. The combined extracts are dried with sodium sulfate, the solvent is removed by suction, and the residue is distilled through a 10-cm Vigreux column in vacuo. Yield 11.10 g (38%), b.p. 74–75°C/0.1 Torr, m.p. 84–86°C. – ^{1}H NMR ($CDCl_3$): δ = 2.98 (s, 3H, CH_3), 2.18–2.15 (s and broad signal, 9H, >CH– and CH_2–C–N), 1.70 (s, 6H, CH_2). – IR (KBr): $\tilde{\nu}$ = 3000–2860 cm^{-1} (CH_3, CH_2, CH), 1675 (C=O), 1485, 1480, 1460, 1450 (CH_3, CH_2), 1220 (C–F). – $C_{13}H_{18}F_3NO$ (261.3): calcd. C 59.77, H 6.90, N 5.36; found C 60.15, H 7.26, N 5.18.

1-(Methylamino)adamantane: A mixture of 10.00 g (0.08 mol) of *N*-adamantyl-2,2,2-trifluoro-*N*-methylacetamide, 30.85 g (0.77 mol) of pulverized sodium hydroxide, and 300 ml of diethylene glycol is heated to 180–190°C for 36 h. After cooling, 300 ml of water is added to the dark mixture, and the solution is extracted five times with 100 ml of diethyl ether. The combined extracts are washed twice with 30 ml of water and then dried with magnesium sulfate. The solvent is removed by suction and the residue is distilled in vacuo. Yield 6.35 g (50%), b.p. 46°C/0.01 Torr, m.p.

243–245°C (as hydrochloride, 244–246°C[19]). – ^{1}H NMR ($CDCl_3$): δ = 1.15 (s, 1H, NH), 2.40 (s, 3H, CH_3), 2.10 (broad, 3H, >CH–), 1.7–1.65 (broad, 12H, CH_2). – IR (KBr): $\tilde{\nu}$ = 3340 cm^{-1} (N–H), 2920–2820 (CH_3, CH_2, CH), 1470, 1450, 1430, 1380 (CH_3, CH_2), 1140 (C–N), 720 (>NH).

1-[(Chloromethyl)amino]adamantane: A suspension of 29.07 g (0.14 mol) of calcium hypochlorite in 350 ml of water is cooled in an ice bath to 0°C. A solution of 14.25 g (86.23 mmol) of 1-(methylamino)adamantane in 120 ml of dichloromethane is added at such a rate that the temp. of the solution remains below 5°C. The mixture is filtered, and the aqueous part of the filtrate is extracted four times with 50 ml of dichloromethane. The combined organic phases are dried with sodium sulfate. The solvent is removed by suction and a yellowish viscous liquid remains. Yield 7.00 g (41%). – ^{1}H NMR ($CDCl_3$): δ = 3.08 (s, 3H, CH_3), 2.3 (broad, 3H, >CH–), 1.95 (d, *J* = 2.4 Hz, 6H, CH_2CHN), 1.8 (d, *J* = 2.4 Hz, 6H, CH_2).

endo-7-[(Methylamino)methyl]bicyclo[3.3.1]nonan-3-one: 7.00 g (35.1 mmol) of 1-[(chloromethyl)amino]adamantane is treated with 11.10 g (83.00 mmol) of aluminium chloride in the same manner as described for **1** in ref.[2]. A mixture of solids is obtained containing (GC-MS analysis) 1-aminoadamantane, 1-(methylamino)adamantane, and 7-[(methylamino)methyl]bicyclo[3.3.1]nonan-3-one. Attempts to isolate the product have failed.

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